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EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	26

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/644,668	Applicant(s) KORMAN ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/28/03, 6/3/03 and 6/12/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-95 and 115-147* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *118-121,124 and 130-133* is/are allowed.

6)☒ Claim(s) *69-95,125-129 and 134-147* is/are rejected.

7)☒ Claim(s) *115-117,122 and 123* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☒ Interview Summary (PTO-413) Paper No(s). 24 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's provision on 3/28/03 of the full preliminary amendment (Paper No. 21) originally provided 1/7/02 (Paper No. 8) is acknowledged with appreciation. The amendments to the specification and to added the sequence listing have been entered. The amendment to the claims were also entered, but have been superceded by the amendment of Paper No. 23.

2. Applicant's amendments, filed 3/28/03 and 6/12/03 (Paper Nos. 23 and 25), are acknowledged.
Claims 69-147 have been added.
Claims 1-68 and 96-114 have been canceled.
Claims 69, 75-80, 86-91 and 115-117 have been amended.
Claims 69-95 and 115-147 *are pending.*

3. Applicant's election without traverse of Group I in Paper No. 23 is acknowledged. Newly added claims 69-147 are acknowledged to correspond to the invention set forth in Group I. Applicant's election of a particular species of antibody that binds CTLA-4 of the 10D1 antibody (SEQ ID NOS as set forth in Table 3 on page 74 of the specification and Figures 5-8) is also acknowledged.

Applicant is advised that the search has been extended to encompass the 1E2 and 4B6 antibodies, as identified by the SEQ ID NOS of Table 3 and Figures 5-8.

Claims 69-95 and 115-147 *are under consideration in the instant application.*

Drawings

4. The drawings submitted 3/28/03 have been approved by the Draftsman.

Priority

5. Applicant's claim for domestic priority under 35 U.S.C. 119(e) to provisional application 60/150,452 (8/24/1999) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 69-95 and 115-147 of this application. In particular, it is noted that although there is support for the genus of human antibodies to human CTLA-4, there does not appear to be an adequate written description of any human antibodies to human CTLA-4 wherein the heavy of light chains are limited to any of the specific sequences or families (i.e., VH 3-30.3, VH 3-33, VK A-27 or VK L5) recited in independent claims 69, 80, 115-121 or 130.

In addition, although certain properties are attributed to the human antibodies to human CTLA-4, not all of the properties recited in independent claim 91 appear to be described in the provisional application. In particular, the Examiner was unable to identify support for the property of not cross-reacting with non-lymphoid tissue.

The effective filing date of the instant claims is therefore considered to be that of the instant application, i.e., 8/24/2000.

Specification

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

It is suggested that Applicant amend the title to -- HUMAN CTLA-4 ANTIBODIES -- .

7. The abstract is objected to for the following informality: Applicant should avoid the use of novel in the abstract, as patents are presumed to be novel and unobvious.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

In particular, it is noted that on page 5 of the specification at lines 16-17 there is a sentence fragment that should be removed.

Claim Objections

9. Claims 122 and 123 are objected to under 37 CFR 1.75 as being substantial duplicates of one another. It appears that claim 123 was intended to recite an alternate binding affinity.

10. Claims 115, 116 and 117 are each objected to because of the following informalities: in each claim section (a) recites "the amino acid sequence set forth in SEQ ID NOS:" when it appears that – SEQ ID NO: -- was intended in view of the single ID No. recited. Appropriate correction is required.

Claim Rejections - 35 USC § 112 first paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 69-95, 125-129 and 134-147 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein. *This is a New Matter rejection for the following reasons*:

Applicant's amendment asserts that no New Matter has been added. However, the specification does not appear to provide an adequate written description of at least one limitation found in each of independent claims 69, 80, 91, 121 and 130. The instant claims now recite limitations which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Independent claims 69 and 80 and claims dependent thereon recite human antibodies which bind CTLA4 and utilize EITHER a heavy chain variable region (claim 69), OR a light chain variable region (claim 80), encoded by a particular gene.

The specification discloses the genus of human antibodies to CTLA4. The specification also discloses:
a) a first subgenus of human antibodies to CTLA4, wherein the antibodies are encoded by the VH3-33 heavy chain variable region gene AND the VK L15 light chain variable region gene; and
2) a second subgenus of human antibodies to CTLA4, wherein he antibodies are encoded by the VH3-30.3 heavy chain variable region gene AND the VK A27 light chain variable region gene.
A single species within the first subgenus is disclosed (the 1E2 antibody), and two species of antibodies within the second subgenus are disclosed (the 10D1 and 4B6 antibodies).

However, it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

In the instant case, there does not appear to be an adequate written description of the subgenus now claimed in independent claims 69 and 80, and claims dependent thereon, permitting multiple light chains to be paired with a particular heavy chain, or vice versa. There does not appear to be adequate description in the specification as filed or original claims of a subgenus defined only in terms of the heavy chain OR the light chain. In addition, although certain dependent claims require both a heavy and light chain, the "or" phrasing still results in combinations (e.g., VH3-30.3 and VK L15) that lack adequate support.

Claim 91 and claims dependent thereon recite the limitation "does not cross-react with non-lymphoid tissue". There does not appear to adequate written support describing a subgenus of the human anti-CTLA4 antibodies that do not cross-react with non-lymphoid tissue. While Table 4 on pages 80-81 does provide evidence that the 10D1 antibody does not cross-react with non-lymphoid tissue, this description of a single species of 10D1 does not appear to be sufficient to describe the subgenus, as set forth above.

Finally, although the subgenus described in independent claim 121 and the subgenus described in independent claim 130 do appear to have adequate written support in the specification as filed, the functional properties recited in dependent claims 125-129 and 134-138 do not. These limitations appear to be described in the specification *only* in the context of the 10D1 antibody. Therefore there does not appear to be adequate support for the subgenus set forth in claims 125-129 and 134-138. These same comments apply to claims 92-95, even were there adequate support for claim 91.

Applicant is required to cancel the New Matter in the response to this Office Action.
Alternatively, Applicant is invited to clearly point out the written support for the instant limitations.

35 U.S.C. §§ 102 and 103

13. The following rejections under 35 U.S.C. §§ 102 and 103 are made under the assumption that the effective filing date for the instantly claimed invention is 8/24/2000, which is the actual filing date of the instant application.

Claim Rejections – 35 U.S.C. §§ 102 and 103

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language

15. Claims 69-74, 77, 80-85, 88, 91-95 and 147 are rejected under 35 U.S.C. 102(a) as being anticipated by Hanson et al. (WO 00/37504, IDS #24).

Hanson et al. teach human antibodies to CTLA4 (see entire document). Hanson et al. teach numerous antibodies to CTLA4 which comprise a heavy chain variable region that is encoded by a VH 3-33 gene (see e.g., clone 4.1.1 of Table II on page 69). Note that the DP-50 gene is a member of the VH 3-33 family (see comment on page 69 at lines 5-10). Table II of Hanson et al. also teaches of number of human antibodies which bind CTLA4 and use the light chain variable region of a human VK A27 gene (e.g., clone 4.1.1).

Table I on page 65 of Hanson et al. teaches that the 4.1.1 antibody (as well as many of the other antibodies) has a binding affinity of about 10^9 M^{-1} or greater (expressed as an association constant, KA, note the units of this measurement, and see page 51 at lines 30-31).

Tables IIIA and IIIB on page 78 teaches that many of the anti-CTLA4 antibodies of Hanson et al. inhibit the binding of human CTLA4 to either B7-1 or B7-2. In view of the IC50s taught in Tables IIIA and IIIB, the 4.1.1 and other antibodies reduce binding of human CTLA4 to each of B7-1 and B7-2 by at least 50% when the concentration of antibody is at least about 1μg/mL (see also pages 77-78 "Materials and Methods").

Hanson et al. also teach that that the 4.1.1 antibody has highly desirable properties, including not cross-reacting with mouse CTLA4 (see page 51 at line 21 to page 52 at line 2, particularly in view of the statement on page 86 at lines 13-16).

Binding of CTLA4 antibodies, including the 4.1.1 antibody, toCTLA4 from cynomologous monkeys is taught at pages 54-55, especially the bridging paragraph of pages 54-55).

In view of the specific binding of the human anti-CTLA4 antibodies of Hanson et al., antibodies including the 4.1.1 antibody would inherently not cross-react with non-lymphoid tissue since human CTLA4 is a lymphoid restricted molecule.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the anti-CTLA4 antibodies of Hanson et al.

The reference teachings thus anticipate the instant claimed invention.

16. Claims 91-92 and 94-95 are rejected under 35 U.S.C. 102(e), or in the alternate under 35 U.S.C. 102(a), as being anticipated Allison et al. (U.S. Pat. No. 6,051,227, IDS#5), as evidenced by Surani et al. (WO 90/04036).

Allison et al. teach the application of antibodies to human CTLA4 that block CTLA4 signaling for the treatment of various human diseases (see entire document, e.g., Abstract).

Allison et al. teach that the antibodies to CTLA4 should block the binding of CTLA4 to its ligands CD80 (B7-1) and CD86 (B7-2), and that the antibodies should bind CTLA4 with an affinity of about 10^{-8} M (see columns 3-5, especially column 4 at lines 15-30 and column 5 at lines 5-12).

Allison et al. teach that for in vivo use in humans, it is particularly desirable to reduce the antigenicity of the antibody by producing the antibody in mice having transgenic human immunoglobulin constant region genes (see column 7, especially lines 39-53).

Allison references Surani et al. (WO 90/04036) for antibodies of reduced antigenicity. Surani et al. teach transgenic mice which can express a fully human antibody after immunization with an antigen (see entire document).

Thus Allison et al. teach a human antibody to human CTLA4 wherein said antibody binds CTLA4 with an affinity of about 10^{-8} M and inhibits binding of human CTLA4 to its ligands B7-1 (CD80) and B7-2 (CD86). Although Allison et al. are silent as to the IC50 of the antibodies for inhibition of binding of B7-1 or B7-2, an antibody with the affinity taught by Allison et al. would necessarily reduce binding of CTLA4 to either B7-1 or B7-2 by at least 50% at a concentration of about 1μg/ml.

Allison et al. also teach that the antibodies should be specific for CTLA4 and substantially unreactive with even related molecules such as CD28 (column 4 at lines 15-22). In view of this specific binding, the CTLA4 specific antibodies of Allison et al. would inherently not cross-react with non-lymphoid tissue since human CTLA4 is a lymphoid restricted molecule.

In addition, because a transgenic mouse is the animal immunized to produce human antibodies to human CTLA4, the mouse would not produce antibodies that could bind mouse CTLA4 since it would be tolerant to mouse CTLA4 as a self antigen. Thus the antibodies taught by Allison et al. include antibodies which do not bind mouse CTLA4.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the anti-CTLA4 antibodies taught by Allison et al.

The reference teachings thus anticipate the instant claimed invention.

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 91-95 and 147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allison et al. (U.S. Pat. No. 6,051,227, IDS#5) in view of Kucherlapati et al. (U.S. Pat. No. 6,075,181, IDS #4).

The claims are drawn to human antibodies that bind human CTLA4 with a binding affinity of at least 10^8 M^{-1} or greater, that inhibit the binding of CTLA4 to B7-1 or B7-2, and that do not cross-react with non-lymphoid tissue.

Allison et al. teach the application of antibodies to CTLA4 that block CTLA4 signaling for the treatment of various human diseases (see entire document, e.g., Abstract).

Allison et al. teach that the antibodies to CTLA4 should block the binding of CTLA4 to its ligands CD80 (B7-1) and CD86 (B7-2), and that the antibodies should bind CTLA4 with an affinity of about 10^{-8} M (see columns 3-5, especially column 4 at lines 15-30 and column 5 at lines 5-12).

Allison et al. teach that for in vivo use in humans, it is particularly desirable to reduce the antigenicity of the antibody by producing the antibody in mice having transgenic human immunoglobulin constant region genes (see column 7, especially lines 39-53).

Although Allison et al. are silent as to the IC50 of the antibodies for inhibition of binding of B7-1 or B7-2, an antibody with the affinity taught by Allison et al. would necessarily reduce binding of CTLA4 to either B7-1 or B7-2 by at least 50% at a concentration of about 1μg/ml.

Allison et al. also teach that the antibodies should be specific for CTLA4 and substantially unreactive with even related molecules such as CD28 (column 4 at lines 15-22). In view of this specific binding, the CTLA4 specific antibodies of Allison et al. would not cross-react with non-lymphoid tissue since human CTLA4 is a lymphoid restricted molecule.

Allison et al. do teach that the anti-CTLA4 antibodies can be human, as noted supra. However, Allison et al. do not teach the utilization of transgenic mice expressing a highly diverse repertoire of human variable regions.

However, the ordinary artisan at the time the instant invention was made would have been motivated to produce fully human antibodies in one of the transgenic mouse models which were then available for production of fully human antibodies.

Kucherlapati et al. teach a mouse model which can be immunized with human antigen to produce human antibodies utilizing any of a number of different human heavy and light chain variable regions (see entire document, e.g., columns 1-2).

Kucherlapati et al. teach that CTLA4 is one of the antigens which can be used to immunize the mice expressing human immunoglobulin genes for the production of fully human antibodies to CTLA4 (see columns 8-9, especially column 8 at lines 46-54).

The ordinary artisan at the time the invention was made would therefore have found it obvious to utilize the mouse model taught by Kucherlapati et al. for the production of fully human antibodies to human CTLA4. The ordinary artisan at the time the invention was made would have been motivated to produce antibodies to human CTLA4 in the mice of Kucherlapati et al. because the mice of Kucherlapati et al. possess most of the human immunoglobulin heavy and light chain variable region genes. Because of this diverse repertoire, the mice of Kucherlapati et al. would produce pairings of heavy and light chains that would have high affinity for the immunizing antigen, particularly after multiple immunizations.

In view of the teachings of Allison et al. regarding the desirable properties of the human antibodies specific for human CTLA4, the ordinary artisan would have been motivated to select those antibodies that bound CTLA4 with high affinity, at least about 10^{-8} M and even higher affinities such as about 10^{-9} M. The ordinary artisan at the time the invention was made and in view of the teachings of Allison et al. would also have selected those human antibodies to human CTLA4 that were able to block binding of human CTLA4 to B7-1 and B7-2, including antibodies of sufficient affinity to block binding by at least 50% when the concentration of antibody was at least about 1μg/ml. The ordinary artisan would have had a reasonable expectation of producing human antibodies to human CTLA4 and selecting those with these desired properties since Kucherlapati et al. provide the methods of making large numbers of antibodies to the antigen of interest and Allison et al. teach those properties which are desirable and the reagents and assays needed to select such antibodies.

In addition, given the art recognized utility of primates, including cynomologous monkeys, in developing and validation of methods of treating humans, the ordinary artisan at the time the invention was made would have been motivated to select for those antibodies that could bind both human and cynomologous CTLA4. Given the close phylogenetic relationship of humans and primates, including cynomologous monkeys, the ordinary artisan at the time the invention was made would have had a reasonable expectation that immunizing a mouse with human CTLA4 would result in antibodies that could bind both human CTLA4 and CTLA4 from closely related species. The ordinary artisan at the time the invention was made would not have a reasonable expectation that antibodies produced in a mouse would also bind the mouse form of the immunizing antigen, because an antibody produced in a mouse which bound mouse CTLA4 would be an autoantibody and B cells producing autoreactive antibodies are normally eliminated. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

19. Claims 115-120 appear to be novel and unobvious as the prior art does not teach or suggest antibodies having the amino acid sequences recited, in particular the CDR3 sequences.

20. Claims 121-124 and 130-133 also appear to be novel and unobvious. Although the art teaches antibodies to CTLA4 that comprise the VH 3-33 heavy chain variable region *or* the VK A27 light chain variable region, the art does not teach the combination of VH 3-33 paired with VK L15 (claim 130) or the combination of VH 3-30.3 and VK A27 (claim 121). In addition, there does not appear to be sufficient motivation for the ordinary artisan to select these particular combinations from the many heavy and light chain variable regions which might possibly be used.

21. Claims 115-117 and 122-123 are objected to for informalities, but would otherwise appear to be drawn to allowable subject matter.

22. Claims 118-121, 124 and 130-133 appear to be allowable.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number for before Final submissions is (703) 872-9306.

Jessica Roark, Ph.D.
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August 22, 2003

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